Remarks

Applicants have amended claims 1, 11, 13, and 38 to a preferred embodiment, namely to methods directed to neoplastic cells. Accordingly, claims 4 and 12 have been cancelled and claim 3 has been amended to perfect the antecedent basis. Support for the amendment can be found, for example in the original claims 4 and 12. Accordingly, no new matter has been introduced by the amendments and their entry is respectfully requested.

Applicants have also amended claims 37 and 38 to perfect the antecedent basis for certain terms as shown in the Listing of Claims. Amendments are clerical, and thus, do not introduce new matter. The entry of the amendments is respectfully requested.

Applicants now turn to the specific rejections.

The Examiner rejected claim 37 as allegedly not complying with 35 U.S.C. §112, second paragraph, definiteness requirement. Specifically, the Examiner noted that there was insufficient antecedent basis for "the non-replicating vector encoding the prodrug activating enzyme" in line 4 of the claim. The Examiner further noted that there was insufficient antecedent basis for "the replicating vector encoding the apoptosis inhibiting agent" on lines 5-6 of the claim. In the Advisory Action, the Examiner did not comment on the 112 rejection of claim 37 at all but refused to enter the amendment. Applicants respectfully request that the amendments be now entered.

In view of the amendments to claim 37, Applicants respectfully submit that the rejection has been obviated.

The Examiner did not present any prior art rejections against claim 37. Accordingly, Applicants respectfully submit that claim 37 is now in condition for allowance.

The Examiner rejected claims 1, 3-13, and 38 under 35 U.S.C. §103(a) as allegedly being unpatentable over Waxman et al. (WO 99/05299) in view of Bilbao et al. (WO 99/55382) for the same reasons already set forth in the Office action mailed on 8/8/07 (pages 6-10).

The Examiner acknowledged that "Waxman et al do not teach methods of killing neoplastic cells further comprising the step of transducing neoplastic cells already transduced with a vector with a vector encoding a heterologous gene with a vector encoding an apoptosis inhibiting agent." (page 8, lines 12-14 of 8/8/07 Office Action).

Examiner then alleged that Bilbao provides this missing part.

Applicants strongly disagree. Bilbao does not teach transducing a neoplastic cell with an antiapoptotic agent. Bilbao described **vectors encoding Bcl-2, an antiapoptotic** molecule**, "to protect** adenoviral transduced **cells, to improve organ preservation** for transplantation**, to protect** from **ischemia/reperfusion injury, to protect cells after** cellular **xenotransplantation, and to protect endothelial cells** from various inducers of injury." (Page 9, lines 23-29, emphasis added). Bilbao did not express the vector in a neoplastic cell. The cells used in Bilbao were **liver cells** (see, example 26). Nothing in the sentence cited by the Examiner on page 9, lines 3-6, of 8/8/07 Office Action ("strategies to prolong the expression of transgene delivered by adenovirus vector, even in the context of diseases in which transient effects may be sought, are essential requirements for achieving clinical utility" citing page 52, lines 6-10 of Bilbao) provides any suggestion that the Bcl-2 encoding vector could be used in neoplastic cells. Bilbao is solely concerned in **preventing apoptosis** of cells for the **purpose of preserving** the cells, such as in the specific application of organ transplantation that the entire application is directed towards.

Accordingly, the missing element as admitted by the Examiner, namely "**transducing neoplastic cells** already transduced with a vector with a vector encoding a heterologous gene with a vector encoding an apoptosis inhibiting agent" simply is not present in Bilbao.

In addition to the crucial missing claim element not being present in the combination of the references, contrary to the Examiner's arguments, Applicants respectfully submit that a skilled artisan would have been taught away from combining Waxman with Bilbao for the purposes of neoplastic cells as described below.

Bilbao teaches that if one expresses Bcl-2 in a cell, **it will survive**. In fact, that is the sole purpose of Bilbao's experiment: to increase survival of the transduced cell. As already described in the Declaration by. Dr. Waxman ("Waxman Declaration"), that is not what one wants in the context of a neoplastic cell (see, e.g., paragraphs 17-18 of the Waxman Declaration). Obviously, a skilled artisan does not want a neoplastic cell to survive. The Examiner provided no evidence to counter Waxman's expert testimony regarding why anyone would want to decrease apoptosis in cancer cells that already typically express high levels of anti-apoptotic molecules as shown in Exhibits A and B (submitted on October 20, 2008), which one typically has wanted to "shut down." Applicants respectfully submit that only a person who has read the present application and results shown in the examples therein can provide an explanation. Therefore, Applicants respectfully submit that the Examiner here applies impermissible hindsight in furthering the arguments regarding obviousness of the present claims.

It is well known that many neoplastic cells express high level of anti-apoptotic molecules (see, e.g. Exhibits A and B). It is also well known that this specific over-expression of anti-apoptotic molecules drives the survival of the neoplastic cells (Exhibits A and B). Thus, as explained in the Waxman Declaration, a skilled artisan would not have even considered adding even more anti-apoptotic agents to cancer cells. On page 55, lines 11-13, Waxman simply states that "some therapeutic enhancement may also be anticipated in tumor cells with high levels of **endogenous** RED expression." The Examiner appears to confuse the natural phenomenon of one of the causes of cancer, namely decreased apoptosis, and the artificial novel cancer treatment of the present invention, namely artificially further decreasing apoptosis in the neoplastic cells in combination with expressing a prodrug activating enzyme. The decrease of apoptosis in cancer cells has led those skilled in the art to conclude that the neoplastic cells need to increase, not decrease, apoptosis to be killed (see, e.g. pars. 17 and 18 of the Waxman Declaration). Contrary to such conventional knowledge, the present invention proposes a method where one adds more antiapoptotic agents to said neoplastic cells in combination of other cancer treatment methods.

The present claims are specifically directed to an embodiment, which requires that neoplastic cells are transduced with the combination of a heterologous gene and anti-apoptotic cells.

On page 9, lines 1-3 of the 8/8/07 Office Action, the Examiner alleges that Bilbao "taught specifically that at least a toxin gene has been selectively delivered for expression in cancer cells to achieve their eradication in a molecular chemotherapy approach" (citing page 2, lines 15-27 of Bilbao). This statement is just wrong. There is nothing in this background section of Bilbao that would teach or suggest that the vector expressing Bcl-2 could be used in **neoplastic cells**.

The Examiner also cited Luo and Wilson. However, the Examiner only states that Luo taught a method in which coexpression of p35 enhanced the inhibition of neointimal formation by Fas ligand via the utilization of Ad2/FasL/p35. Thus, there is nothing in Luo that would provide motivation for a skilled artisan to **transduce p35 in a neoplastic cell.** Also Wilson only describes a method for gene transfer comprising the step of exposing a population of host cells both *in vitro* and in a mammalian patient (e.g., hepatocytes, lung, muscle, epithelial cells) to a recombinant viral vector, which comprises a gene encoding an anti-apoptotic agent (e.g., Bcl-2) and a transgene (e.g., a transgene encoding a growth hormone, erythropoietin, factor IX, or liver enzymes such as ornithine transcarbamylase, arginase and others). **None of the cells used in Wilson were neoplastic cells**. Thus, there is nothing also in Wilson that would provide a teaching, a motivation, or expectation of success for a skilled artisan to use an apoptosis-inhibitor, such as Bcl-2 **in transducing neoplastic cells**, wherein, according to the skilled artisans at the time of the filing, one wanted **to induce, not inhibit** apoptosis.

Although Bilbao **shows** that Bcl2 can prolong transgene expression **in normal cells**, Bilbao does **not show** or suggest that Bcl2 or any other anti-apoptotic factors can do so **in cancer cells**. Indeed, as already discussed in the Waxman Declaration, at the time of the present invention, the expectation was that anti-apoptotic factors would **not** be effective in prolonging transgene expression in cancer cells, insofar as cancer cells already express high levels of anti-

apoptotic factors, such as Bcl2. Therefore, one would have been taught away from combining Bilbao with Waxman.

Moreover, it was unexpected that tumor cells expressing the prodrug-activating P450 enzyme together with an anti-apoptotic factor would eventually die following prodrug treatment, insofar as the active form of the P450 prodrug was known to kill cancer cells by an apoptotic mechanism. This unexpected finding indicates that the activated prodrug is eventually able to circumvent the anti-apoptotic factor and kill the cancer cells by a slower, alterative (i.e., a non-apoptotic) mechanism.

Applicants respectfully submit that the Examiner's comment (p. 6, lines 5-7) that Bilbao et al taught that "at least a toxin gene has been selectively delivered for expression in cancer cells to achieve their eradication in a molecular chemotherapy approach (page 2, lines 15-27)" is taken out of context. Bilbao made this statement in the context of background information about gene therapy. However, Bilbao does not state, or even imply, that Bcl2 may be useful in enhancing toxin gene therapy for cancer cell treatment.

Further supporting Dr. Waxman's Declaration, Applicants submit herewith two review articles (Exhibits A and B) as examples that specifically support the arguments made by Dr. Waxman regarding the state of the art of the role of apoptosis in cancer. Both of these, and numerous other articles all conclude that **lack of apoptosis is a severe problem in cancer**. Thus, as already stated by Dr. Waxman, no one in their right mind would have thought of exacerbating the problem by promoting even more lack of apoptosis to treat cancer (see, e.g., pars. 17-18 of the Waxman Declaration).

In view of the above, Applicants submit that the rejection of claims 1, 3-13, and 38 under 35 U.S.C. 103(a) over Waxman in view of Bilbao is improper and should be withdrawn.

The Examiner rejected claims 14-18 and 31-33 under 35 U.S.C. 103(a) as allegedly being unpatentable over Waxman in view of Bilbao and further in view of Robertson and Griffith.

Applicants respectfully disagree and submit that the rejection be withdrawn for the following reasons.

The combination of Waxman and Bilbao has been discussed above. The addition of Robertson and Griffith fails to provide the missing motivation to combine Waxman with Bilbao.

All Robertson described is the use of a recombinant viral vector expressing various anti-apoptotic polypeptides such as NAIP, HIAP, HIAP2, XIAP and other under the control of a regulatable promoter to inhibit death of a cell of the nervous system in a patient. Griffith only taught a method of **inducing tumor cell apoptosis** using Trail/Apo2-L gene transfer in a mammal, and optionally in combination with chemotherapeutic agents, radiotherapeutic agents or immune potentiating genes or proteins. Thus, even Griffith provides support for the state of the art declaration by Dr. Waxman in describing that they **used tumor cell apoptosis inducing**, not **inhibiting** agents.

Therefore, contrary to the Examiner's argument, there was nothing in these two references that would have taught a skilled artisan to use the cancer treatment method as claimed.

In view of the above, Applicants submit that the rejection of claims 14-18 and 31-33 under 35 U.S.C. 103(a) over Waxman in view of Bilbao and further in view of Robertson and/or Griffith is improper and should be withdrawn.

The Examiner further rejected claims 1 and 3-6 (with respect to the elected species p35) under 35 U.S.C. 103(a) as being unpatentable over Waxman in view of Bilbao, and further in view of Beidler for the same reasons already set forth in the Office action mailed on 8/8/07.

Applicants respectfully disagree and submit that the rejection be withdrawn for the following reasons.

The combination of Waxman and Bilbao has been discussed above. Neither Robertson nor Griffith provide the missing motivation to combine Waxman with Bilbao.

All Beidler described is that the baculovirus p35 protein is able to interrupt a highly conserved and ubiquitous component of the death machinery because p35 inhibits TNF- and Fas-induced apoptosis, blocks the cleavage of PARP, a death substrate in the apoptotic pathway as well as blocking developmental, viral, and x-irradiation-induced cell death. There is no mention in Beidler that p35, or any other anti-apoptotic molecule would be useful for the treatment of cancer.

Therefore, contrary to the Examiner's argument, there was nothing in Beidler that would have taught a skilled artisan to use the cancer treatment method as claimed.

In view of the above, Applicants submit that the rejection of claims 1 and 3-6 under 35 U.S.C. 103(a) over Waxman in view of Bilbao and further in view of Beidler is improper and should be withdrawn.

In view of the foregoing amendments, arguments and evidence, Applicants respectfully submit that all claims are in condition for allowance. Early and favorable action is requested.

In the event that any additional fees are required, the Commissioner is authorized to charge Nixon Peabody LLP Deposit Account No. 50-0850.

Date: January 20, 2009

Respectfully submitted,

/Leena H. Karttunen/

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